REMARKS/ARGUMENTS

With entry of this amendment, claims 1-14 and 16-28 are pending in the above-identified application. Claims 13, 14, and 16-25 have been withdrawn by the Examiner as drawn to a non-elected invention. Claims 1 and 12-14 are amended and claims 26-28 are added as set forth in detail below. Support for these amendments are identified in the following remarks. No new matter is added by these amendments. Examination and reconsideration of all pending claims are respectfully requested.

The Examiner has denied entry of the substitute specification because the Examiner believes pages 24 and 25 to constitute new matter. The Examiner has stated that pages 24 and 25 would be entered if Applicants submit evidence that these pages were filed with the original application. Applicants have attached hereto a receipt postcard for filing of the instant application, which shows that 26 pages of description were filed with the application on February 29, 2000. The description as filed contains a total of 26 pages only when pages 24 and 25 are included. Accordingly, Applicants respectfully request that the Examiner enter the substitute specification.

The Examiner has maintained the requirement for a new oath or declaration because the substitute specification has been denied entry. Because the substitute specification does not include new matter for the reasons set forth above, Applicants believe that the requirement for a new oath or declaration is obviated.

Rejections under 35 U.S.C. §112, second paragraph

The Examiner has maintained the rejection of claim 6 under 35 U.S.C. §112, second paragraph, as being allegedly vague and indefinite for reciting "substantially all" with respect to the immunological reactivity retained by the modified peptide relative to the unmodified peptide of claim 1. The Examiner states that pages 5 and 12 of the specification,

referred to in Applicants' previous response dated October 23, 2002, "do not discuss how the claimed modifications impact the 'immunological reactivity' of the peptide."

The Examiner appears to have misunderstood the remarks provided in Applicants' previous response. Therefore, in addition to providing additional argument, Applicants clarify these remarks as set forth hereinbelow.

First, pages 5 and 12 of the specification were not cited for disclosure of how the recited modifications to peptides of the present invention "impact" immunological reactivity of the peptides. Rather, these pages were cited because the disclosure provided therein, together with the disclosure generally provided in the specification as a whole, provide a standard to the skilled artisan for determining that degree of immunological activity which is "substantially all" of the reactivity of the unmodified peptide, as recited in claim 6, including, *e.g.*, assays using modified peptides for measuring immunological reactivity.

As stated in the MPEP, the fact that a term of degree may not be precise "does not automatically render the claim indefinite under 35 U.S.C. § 112, second paragraph." MPEP § 2173.05(b), *citing Seattle Box Co. v. Industrial Crating & Packing, Inc.*, 221 USPQ 568 (Fed. Cir. 1984). Instead, as noted previously, whether a claim is definite depends on whether those skilled in the art would understand the scope of the claim when the claim is read in light of the specification. *See North Am. Vaccine, Inc. v. American Cyanamid Co.*, 28 USPQ2d 1333, 1339 (Fed. Cir. 1999); *see also* MPEP § 2173.05(b). In particular, during patent examination, when a term of degree is presented in a claim, "a determination is to made as to whether the specification provides some standard for measuring that degree." *Id.* (emphasis provided). If so, then the claim is not indefinite. Even if a standard is not provided, the claim is not indefinite if one of ordinary skill in the art, in view of the prior art and the status of the art, would be nevertheless reasonably apprised of the scope of the invention. *See id.*

In the present case, the specification provides a standard for determining whether a modified peptide retains "substantially all" of the immunoreactivity of the unmodified peptide. As stated in the specification, "the polypeptide employed in the subject invention need not be

identical to any particular HIV-1 or HIV-2 polypeptide sequence, so long a the subject compound is able to ***immunologically mimic*** an epitope of the pol region of at least one of the strains of the HIV-1 or HIV-2 retrovirus." (Specification at page 5, lines 4-7 (emphasis provided).) The term "immunologically mimic" is a term of art, well-known to the skilled artisan as of the effective filing date of the present application, and refers, *inter alia*, to the ability of a molecule (*e.g.*, a peptide) to specifically cross-react with antisera raised against another molecule. In view of this disclosure in the specification, the skilled artisan would reasonably understand the phrase "substantially all of the immunological reactivity of the unmodified polypeptide" to mean that degree of immunological reactivity which allows the modified peptide to immunologically mimic the corresponding epitope of the pol region of at least one of HIV-1 and HIV-2. This degree of immunological reactivity can easily be determined using routine assays, such as, *e.g.*, those disclosed in the specification, to measure cross-reactivity of the modified peptide against antibodies to the corresponding pol epitope.

Accordingly, at least for the reasons set forth above, claim 6 is not believed to be indefinite under 35 U.S.C. § 112, second paragraph.

Rejections under 35 U.S.C. § 102

Claims 1, 3, 5-9 and 12 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Kang (U.S. Patent No. 5,858,646). The present rejection is traversed in part and overcome in part as set forth below.

Amended independent claims 1 and 12 now recite, *inter alia*, "contacting ... the body fluid with a composition containing at least one polypeptide having one of the following polypeptide sequences... (III) BRU124F1X (SEQ ID NO: 3) ...." Support for this amendment is found throughout the specification and particularly in the Examples.

Kang does not disclose the method recited in claims 1 and 12 as amended. Kang discloses an ELISA assay for detection of HIV antibodies using the product of the HIV pol gene, or a substantial portion thereof. (*See* Kang at, *e.g.*, Example 3; column 1, lines 54-58; and

column 2, lines 10-17.) The Examiner refers to SEQ ID NO:5, which discloses amino acid sequence encoded by one particular strain of HIV-1 (HIVBRU). The sequence set forth in SEQ ID NO:5 contains 1016 amino acid residues. (*See id.* at columns 55-60.) Because a polypeptide of 1016 amino acid residues is considerably larger than the size of a polypeptide of the present invention and can contain any number of epitopes. Kang does not anticipate claims 1, 3, 5-9 and 12.

Rejections under 35 U.S.C. § 103

Cosand in view of Kang

Claims 2, 10, and 11 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Cosand (U.S. Patent No. 5,075,211) in view of Kang. The Examiner states that Cosand "does not expressly teach a method for detecting HIV by contacting a body fluid with a polymerase protein that comprises all forty amino acids of SEQ ID NO:3." The Examiner contends that Kang "overcomes this deficiency by teaching an immunoassay that detects HIV antibody using a substantial portion of the HIV-pol protein, including SEQ ID NO:3." For the reasons set forth below, the instant rejection is traversed in part and overcome in part.

A *prima facie* case of obviousness requires, *inter alia*, a teaching or suggestion in the prior art reference (or references, when combined) of all claim limitations. MPEP § 2143. In the present case, amended claim 1, from which claims 2, 10, and 11, depend, recites "contacting ... the body fluid with a composition containing at least one polypeptide having one of the following polypeptide sequences... (III) BRU124F1X (SEQ ID NO: 3) ...." Neither Cosand nor Kang teach or suggest a polypeptide having the amino acid sequence set forth in SEQ ID NO:3. Therefore, at least for these reasons, a *prima facie* case of obviousness has not been established with respect to claims 2, 10, and 11.

Further, Applicants submit that claims 2, 10, and 11 are nonobvious over Cosand and Kang because the immunological properties of the claimed polypeptide are unexpected.

(*See, e.g., In re Corkill*, 226 USPQ 1005 (Fed. Cir. 1985) (stating that a "greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness"); *see also* MPEP § 716.02.) In particular, we note that immunological reactivity of the polypeptide BRU124F1X (having the amino acid sequence set forth in SEQ ID NO:3) is substantially superior, in terms of both its strength and consistency of reactivity across different HIV positive sera, than the polypeptide of Cosand. Moreover, the degree of this superiority, as of the effective filing date, would be unexpected in view of, *e.g.*, the relative degree of amino acid conservation of the corresponding regions of the pol gene product among the different, known strains of HIV-1

Applicants respectfully refer the Examiner to Table 1A of the instant specification, which shows, *inter alia*, the reactivity of BRU124F1X (of the instant invention, hereinafter "F1X") and BRU124E1 (having SEQ ID NO:1, corresponding to the polypeptide of Cosand, hereinafter "E1") with various HIV-1 positive samples. Applicants note that when the measured $OD_{450/630}$ readings for the HIV-1 positive sera are averaged for each of the peptides, F1X exhibits a mean value of 1.777, as compared to 1.377 for E1. In particular, Applicants note that for E1, two of the eight samples exhibited relatively low $OD_{450/630}$ readings only 2-2.5 times above the cut-off (0.507 and 0.606 for GS91-037 and GS91-034, respectively), while the lowest readings for F1X, for the same sera, were over four to almost seven times above the cut-off value (1.000 and 1.584). In addition, only three samples (37.5%) exhibited very strong readings greater than 1.800, as compared to six of the eight samples (75%) for F1X. Further, standard deviations in $OD_{450/630}$ readings calculated for each of the peptides show that F1X demonstrates substantially greater consistency in immunoreactivity across the various samples (SD = ± 0.348) as compared to E1 (SD = ± 0.575).

This superior immunoreactivity of the F1X peptide relative to E1, as described above, would have been unexpected by the skilled artisan as of the effective filing date of the instant application. First, the skilled artisan would not have expected the difference in immunoreactivity based on the degree of amino acid conservation for the HIV1 pol region corresponding to these peptides. Alignments of the encoded pol gene product for the various strains of HIV-1, known as of the effective filing date of the application, show absolute

conservation of about 46% of the 30 amino acids that constitute the E1 peptide of Cosand. (*See* HIV1 POL Protein Alignment Summary Table (attached hereto, p. II-A-31, at amino acids corresponding to WEAU160 934-963), from *The Human Retroviruses and AIDS 1997 Compendium*, available at The HIV Sequence Database website at http://www.hiv.lanl.gov/content/hiv-db/HTML/compendium.html.) The same alignments show about the same degree of conservation, only about 40%, for the 10 additional amino acids of the F1X peptide of the present invention. (*See id.* at amino acids corresponding to WEAU160 964-973.)

In addition, although F1X contains ten additional amino acids relative to E1, this additional length is too short for the skilled artisan to have expected a substantially greater immunoreactivity of F1X based on the relative sizes of the peptides alone. Furthermore, nothing in the cited art points to these ten additional amino acids as conferring any advantage. In particular, the cited art would not have suggested to the skilled artisan that the ten additional, carboxy-terminal amino acids of the F1X peptide would confer the superior immunoreactivity to the degree shown in the specification.

Therefore, at least for the reasons set forth above, the methods as presently recited in claims 2, 10, and 11 are not obvious over Cosand in view of Kang under 35 U.S.C. § 103.

Montagnier in view of Kang

Claim 4 stands rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Montagnier *et al.* (U.S. Patent No. 5,221,610) ("Montagnier") in view of Kang. Applicants respectfully traverse.

As set forth above, a *prima facie* case of obviousness requires, *inter alia*, a teaching or suggestion in the prior art references of all claim limitations. MPEP § 2143. In the present case, amended claim 1, from which claim 4 depends, recites "contacting ... the body fluid with a composition containing at least one polypeptide having one of the following polypeptide sequences... (III) BRU124F1X (SEQ ID NO: 3) ...." Neither Montagnier nor Kang

teach or suggest a polypeptide having the amino acid sequence set forth in SEQ ID NO:3. Therefore, at least for these reasons, a *prima facie* case of obviousness has not been established with respect to claim 4.

Other Claim Amendments

Claims 13 and 14, which have been withdrawn by the Examiner, are amended to correspond to amended claims 1 and 12 by reciting "... at least one polypeptide having one of the following polypeptide sequences..."

New Claims

Claims 26-28 are added to more fully claim novel aspects of the present invention. Independent claim 26 sets forth a method for determining the presence of antibodies to HIV in a body fluid, comprising, *inter alia*, "contacting, under conditions which permit immunospecific binding to form a reaction mixture, the body fluid with a composition containing a combination of HIV-1 and HIV-2 envelope and polymerase polypeptides," wherein said mixture comprises "at least one HIV-1 envelope polypeptide; ... at least one HIV-2 envelope polypeptide; ... at least one HIV-1 polymerase polypeptide having a polypeptide sequence selected from the group consisting of [(II) BRU124EX (SEQ ID NO: 2), (III) BRU124F1X (SEQ ID NO: 3), and (IV) BRU124F3X (SEQ ID NO: 4)] and ... at least one HIV-2 polymerase polypeptide having a relatively short size and comprising a polypeptide sequence selected from the group consisting of [(V) ROD 124E1 (SEQ ID NO: 5); (VI) ROD 124EX (SEQ ID NO: 6), (VII) ROD 124C2X (SEQ ID NO: 7), (VIII) ROD 124C1X (SEQ ID NO: 8), (IX) ROD 123C3X (SEQ ID NO: 9), (X) POL2A1 (SEQ ID NO: 10), and (XI) ROD124C5X (SEQ ID NO: 11)] ...." Dependent claims 27 and 28 are added to recite particular embodiments of the method of claim 26. Support for these claims are found throughout the specification including, *e.g.*, page 22, lines 12-15; pages 23-25; and page 26, lines 1-17.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,

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Inventor(s): Patrick F. Coleman et al.
Title: SYNTHETIC ANTIGEN FOR THE DETECTION OF ANTIBODIES IMMUNOREACTIVE WITH HIV VIRUS

_____ Declaration _____ Power of Attorney
_X_ Combined Declaration & Power of Attorney
_X_ Assignment _____ Small Entity Decl.
Petition to Extend Time, Revocation and Substitution of Power of Attorney

No. Pages of Description: 26
No. Pages of Appendix: _____
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